CISPLATIN & CAPECITABINE

Loco-regional or metastatic recurrence of H&N SCC after radical surgery or radiotherapy

Drugs/Dosage:	Cisplatin	80mg/m^2	IV	Day 1
	Capecitabine	1000mg/m^2	PO	twice daily from Day 1 to Day 14, followed by 7 days' rest (i.e. 21 day cycle) (often one dose only given on Day 1 (pm), with the the last dose on the morning of Day 15)

Administration: Capecitabine tablets (available as 500mg and 150mg) should be swallowed whole with water within 30 minutes after a meal.
Information, provided by Roche, is available via Pharmacy regarding dispersing the tablets for those patients with swallowing difficulties or with feeding tubes.

Cisplatin: 1 litre 0.9% sodium chloride + 20mmol KCl + 10mmol $MgSO_4$ IV over 2 hours
Mannitol 20% 100ml IV over 15 minutes
Cisplatin in 1 litre 0.9% sodium chloride IV over 3 hours
1 litre 0.9% sodium chloride + 20mmol KCl + 10mmol $MgS0_4$ IV over 2 hrs
500ml 0.9% sodium chloride IV **or** 500ml - 1 litre water orally over 1 hour

Frequency: 3 weekly cycle for 6 cycles

Main Toxicities: myelosuppression; neuropathy / ototoxicity; stomatitis/mucositis; diarrhoea; cardiotoxicity due to capecitabine (see Comments); alopecia (mild); nephrotoxicity; palmar-plantar erythema; ovarian failure/infertility

Anti- emetics: Day 1 highly emetogenic; Days 2 – 14 mildly emetogenic

Extravasation: cisplatin is a non -vesicant

Regular Investigations:	FBC	Day 1
	LFTs & U&Es	Day 1
	Mg^{2+} and Ca^{2+}	Day 1
	EDTA	prior to 1st cycle

Comments: If patient has any baseline hearing problems, carboplatin AUC 5 should be substituted for cisplatin, administered as discussed below under Renal Impairment.

For patients on Cycle 1 whose EDTA is not yet available, Cockcroft & Gault may be used to predict GFR. Cisplatin dose should be adjusted if necessary once EDTA available. EDTA should only be repeated if the result is borderline at the start of treatment or if there is a 30% change in serum creatinine.

Weight should be recorded prior to and at the end of cisplatin treatment, and a strict fluid balance chart should be maintained. An average urine output of at least 100ml/hr must be maintained throughout treatment, and cisplatin infusion should not be commenced unless this urine output is achieved. If the urine output is inadequate, the patient should be assessed and urine output increased by administering 500ml sodium chloride 0.9% IV +/- furosemide 20 – 40mg. Furosemide 20 – 40mg po may also be given if there is a positive fluid balance of 1.5 litres, a weight gain of 1.5kg or symptoms of fluid overload. The patient should be asked to drink 2 litres of fluid in the 24hrs following treatment, and to contact the hospital if this is impossible because of problems e.g. nausea and vomiting.

Reason for Update: overdue review; WBC cut-off removed	Approved by Consultant: Dr S Whitaker
Version: 3	Approved by Lead Chemotherapy Nurse: P Deery
Supersedes: Version 2	Date: 7.2.17
Prepared by: S Taylor	Checked by: C Tucker

Check electrolytes – additional supplementation of magnesium, calcium or potassium may be required.

Fluoropyrimidine therapy has been associated with cardiotoxicity (including myocardial infarction, angina, arrhythmias, cardiogenic shock, sudden death and ECG changes). Therefore, exercise caution in patients with prior history of coronary heart disease, arrhythmias and angina pectoris.

Dose Modifications

Haematological Toxicity:	Neutrophils < 1.5 x 10^9/l or Platelets < 100 x 10^9/l	Delay by 1 week. Repeat FBC and, if normal, resume treatment at full dose.

If there is a 2 week delay due to low FBC, consider a dose reduction of cisplatin +/- capecitabine for remaining cycles. If in doubt, discuss with Consultant.
If patient suffers an episode of Grade 3 febrile neutropenia at any time, continue after recovery with 25% dose reduction for both cisplatin and capecitabine. For any Grade 4 neutropenic sepsis, discuss with Consultant before proceeding.

Non-Haematological Capecitabine Toxicities:

Note that severe diarrhoea and/or severe mucositis early in the first treatment cycle can be the first presenting toxicity due to DPD enzyme deficiency, in which case potentially fatal neutropenia can quickly follow.

Toxicity due to capecitabine may be managed symptomatically and/or modification of the dose (treatment interruption or dose reduction). Use the table below for dose adjustment guidelines. Once the dose has been reduced, it should not be increased at a later time. Doses of capecitabine omitted for toxicity are not replaced or restored. Instead the patient should resume the planned treatment cycle.

Non-Haematological Dose Adjustment Guidelines for Capecitabine according to CTC

Common Toxicity Criteria*	During Course of Therapy	Dose adjustment for next cycle (% of start dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2: 1st Appearance	Interrupt until resolved to Grade 0 – 1	Give 100% dose
Grade 2: 2nd Appearance	Interrupt until resolved to Grade 0 – 1	Give 75% dose
Grade 2: 3rd Appearance	Interrupt until resolved to Grade 0 – 1	Give 50% dose
Grade 2: 4th Appearance	Discontinue treatment permanently	
Grade 3: 1st appearance	Interrupt until resolved to Grade 0 – 1	Give 75% dose
Grade 3: 2nd appearance	Interrupt until resolved to Grade 0 – 1	Give 50% dose
Grade 3: 3rd appearance	Discontinue treatment permanently	
Grade 4: 1st appearance	Discontinue permanently **or, with Consultant approval,** interrupt until resolved to Grade 0 – 1	Give 50% dose

Renal Impairment: NB. Cisplatin is both eliminated primarily (> 90%) in the urine and is itself nephrotoxic. If significant renal toxicity, this must be discussed with the Consultant.

GFR (ml/min)	Cisplatin Dose
≥ 60	Give 100% dose
45 – 59	Give 75% dose
44 – 20	Cisplatin contra-indicated Carboplatin AUC 5, administered in 250ml 5% Glucose over 30 minutes, may be substituted. It may be given according to this protocol, with however no requirement for pre- or post-hydration, nor fluid balance/urine monitoring
< 20	Carboplatin contra-indicated

Carboplatin dose should be calculated using the Calvert Formula:
Dose = Target AUC x (25 + GFR)

CrCl (ml/min)	Capecitabine Dose
> 50	Give 100% dose
30 – 50	Give 75% dose
< 30	Omit

Hepatic Impairment: If bilirubin > 3 x ULN or ALT/AST > 2.5 ULN, omit capecitabine until liver function recovers.

References:
Hitt, R et al; Br J Cancer 2004; 91: 2005 – 2011
Chung, J et al; Eur J Cancer Suppl 2005; 3 (2): Abstract 1030
Lorusso, V et al; JCO 2007; 25 (18S): Abstract 16502